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General Recommendations

by DHEW Subcommittee on Health Effects of PCBs and PBBs *

General

More complete and additional metabolism studies with various individual PCBs and PBBs should be undertaken. Attention to the formation of possible toxic metabolites of these compounds should be considered, as well as detecting and quantifying any specific biochemical parameters which may be affected as a result of such exposures. Based on the above, lifetime feeding studies should be conducted with selected commercial PCBs and PBBs mixtures, as well as selected individual PCBs and PBBs.

Why some species seem to be more susceptible to the toxic effects of PCBs, and which are most closely related to man in their response should be determined. In addition, more experimental data are needed for the occupational PCBs settings; i.e., via the respiratory or dermal route. Additional toxicological evaluations should be made of fish and other foods which contain high levels of environmentally accumulated PCBs and other contaminants. Appropriate toxicological studies should be undertaken with PBBs in order to be able to make some predictions on possible human effects.

The quantitative evaluation of halogenated biphenyl exposure to man with respect to blood and body fat levels, and any possible health effects, needs further study. With respect to PCBs, this may be accomplished by identifying a population of individuals consuming large amounts of fish contaminated with high levels of PCBs. In addition, those exposed industrially should be included in these efforts. With respect to PBBs, appropriate studies should be initiated with Michigan farm families exposed through consumption of contaminated meat and dairy products.

Individual chemical components of PCB residues should be qualitatively identified and procedures for improving quantitation of these residues should be investigated. Commercial PCB (and PBB) mixtures need to be analyzed further to determine which chlorinated dibenzofurans (or, in the case of PBBs, whether any brominated dibenzofurans) are present as contaminants. Specific chlorinated dibenzofuran compounds must by synthesized for use in development of analytical procedures and to aid in identification of contaminants. Analytical procedures are needed to permit examination of foods for presence of chlorinated dibenzofurans. Toxicological studies should be carried out on chlorinated dibenzofurans and brominated dibenzofurans.

Detailed Recommendations

Chemistry

Procedures such as those of Webb and McCall (*1*) should be investigated for possible improvement of the quantitation step in the analysis of PCB residues.

Present procedures for analysis of PCBs yield a "PCB residue" that is commonly examined by use of electron-capture gas chromatography (GC). Individual components of this residue should be identified, and it should be determined whether any of the electron-capture GC peaks can be attributed to Cl-DBFs or Cl-naphthalenes.

Commercial PCB mixtures, such as Aroclors, should be analyzed to determine which Cl-DBFs are

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present as contaminants. Qualitative and (where possible) quantitative studies should be carried out.

Synthesized, individual chlorobiphenyls should be examined for presence of chlorinated dibenzofurans before metabolism or toxicity studies are carried out with the biphenyl. (The importance of this is shown by the reported formation of 2,3,7,8-tetrachloro- DBF as a side-product in the Ullmann coupling reaction used to synthesize the symmetrical 2,2′,4,4′,5,5′-hexachlorobiphenyl.)

A range of Cl-DBFs to be used for analytical procedure development as reference standards for confirmation purposes and for suitable toxicological studies should be synthesized, purified and characterized by physical and chemical methods.

A suitable procedure for analysis of edible fish for Cl-DBFs, emphasizing recovery and quantitation of 2,3,7,8-tetrachlorodibenzofuran, should be developed.

A commercial mixture of brominated biphenyls (FireMaster BP-6) should be analyzed for brominated dibenzofuran content.

Long-used heat exchange, transformer, and capacitor fluids should be analyzed for the presence of chlorinated dibenzofurans.

Specific 14C- or tritium-radiolabeled chlorinated biphenyls that may be needed for toxicity and metabolism studies should be synthesized.

The reported conversion of certain chlorinated biphenyls to Cl-DBFs under sunlight or sunlight-simulating conditions should be studied. If feasible, the work should be extended to additional Cl-biphenyls.

By simulating conditions applicable to heat exchange units and/or transformers, it should be determined whether Cl-DBF content of PCB mixtures increases when the PCB are heated and/or exposed to air.

Laboratory studies under simulated environmental conditions should be performed to determine alteration products from Cl-DBFs when irradiated or heated.

Metabolism and Biochemical Toxicity

Long-term feeding studies approaching life-time should be conducted with the less chlorinated PCB formulations. These studies should include at least two of the less chlorinated PCB formulations and a series of carefully selected individual PCBs.

Further and more complete metabolism studies should be done with the more highly chlorinated PCBs, for comparison with those done with PCBs having five or less chlorine atoms.

The effect of chlorine position on PCB metabolism and arene oxide formation should be further elucidated.

The formation of specific chlorinated dibenzofurans as possible PCB metabolites should be studied, their biochemical toxicity in mammalian species determined, and the magnitude of their toxicity ascertained. These studies will also include those specific chlorinated dibenzofurans identified in new and used PCBs.

If possible, arene oxide metabolites of several PCBs should be synthesized and their toxicology investigated.

Within an isomeric series of PCBs (e.g., tetra- or hexachloro), metabolism of the more toxic members should be compared to those which are less toxic.

Metabolism of individual PBBs, comparable to those for PCBs, should be studied. These data should be related to known toxicities.

The toxicology of known PCB metabolites should be studied.

Porphyrin excretion by the people and animals exposed in the Michigan PBB incident should be checked.

People who are suspected to have received high exposures of PCBs or PBBs should be checked for any changes in enzyme levels—e.g., protein-bound iodine, antipyrene metabolism, serum cholesterol, etc.

The adsorption, distribution and excretion studies of halogenated dibenzofurans and PBBs should be studied.

Further studies of possible PCB metabolism by fish.

The degree of chlorination and length of exposure on the estrogenic effects and reproductive organs, with particular emphasis on the lower chlorinated PCBs (e.g. 1016), should be studied.

Animal Toxicology

Inhalation studies with "heated" PCB mixtures simulating occupational exposure and dermal toxicity studies should be conducted.

Studies as to why some species seem to be more susceptible to the toxic effects of PCBs than others and of these species, which are most closely related in their response to humans should be undertaken.

Subacute and chronic toxicity studies should be conducted with hexabromobiphenyl (FireMaster FF-1) in order to be able to make some predictions on human PBB toxicity.

The toxicity of fish containing high levels of PCBs which have been accumulated by environmental exposure should be evaluated. It should be established whether and which toxic impurities are pres-

ent in used PCBs, such as transformer oil and capacitor fluid.

Long-term feeding studies, approaching life-time, should be conducted with laboratory animals and selected commercial mixtures of PCBs and PBBs as well as selected individual PCBs and PBBs.

Further and more complete metabolism studies should be done with individual PCBs and PBBs. The formation of toxic metabolites of these compounds should be considered and carefully investigated.

Efforts to detect and quantitate specific biochemical mechanisms which are affected or altered by exposure to PCBs or PBBs should be continued.

Human Exposure

Polychlorinated Biphenyls. A population of "fish eaters," who are consuming substantial amounts of fresh water fish with high levels of PCBs, should be identified. This study population should be followed prospectively with adequate dietary histories, blood and body fat levels of PCBs, a health questionnaire, liver function tests, and other biochemical studies.

A similar study should be carried out in an industrial population exposed to PCBs.

Systematic studies to identify subgroups of the total U. S. population who consume high levels of fish with more accurate measures of PCB exposure should be performed.

Polybrominated Biphenyls. A large-scale epidemiological study should be carried out to identify all farm family members from quarantined farms in Michigan, to identify those individuals with secondary exposure to PBB contamination through the purchase of dairy products from quarantined farms on a regular basis, and to compare these groups with a suitable control group of nonexposed farm families. These groups should be followed to assess any short and long term adverse health effects related to PBB exposure.

Subgroups of these farm families from quarantined farms should be studied by: repeat PBB blood levels, matched blood-body fat PBB levels, pregnant female-infant studies, and a battery of biochemical studies.

Ancillary Studies

Toxicology studies in nonhuman primates and rodents with hexabrominated biphenyl and any brominated contaminants of hexabrominated biphenyls are recommended.

Toxicology studies in several animal species (mice, rats, dogs, nonhuman primates) should be carried out on hexabrominated biphenyl and several PCBs to determine species differences in response to the effects of these compounds.

Toxicology studies with feeding of hexabrominated biphenyls and selected PCBs, singly and in combination, should be performed to determine if there are different or additive effects when fed in combination.

REFERENCES

1. Webb, R. G., and McCall, A. C. Quantitative PCB standards for electron capture gas chromatography. J. Chromatogr. Sci. 11: 366 (1973).